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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
ZOLTAN JONES, ALEXANDRA	
ART UNIT	**PAPER NUMBER**
1646	

DATE MAILED: 10/27/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/027,400	WILLIAMS ET AL.	
	Examiner	Art Unit	
	Alexandra Zoltan-Jones, PhD	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 September 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *56-61* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *56-61* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Sob

Response to Amendment

The amendment filed 9/16/2005 has been made of record. Previously pending claims 31, 32, 37-55 have been cancelled. Claims 56-61 are new and are considered for examination. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 57-61 are rejected for being vague and indefinite. Claim 57 is self-referential. Claims 58-61 depend on claim 57. In the interest of compact prosecution, claims 57-61 will be interpreted to depend on claim 56. Appropriate correction is required.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

New claims 56-61 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kazlauskas *et al* (Cell, Vol 58: 1121-1133 [1989]) in view of Kolesnick *et al.* (US Patent #6040149, Filed 1/10/1997) and further in view of Gronwald *et al.* (Proc Natl Acad Sci USA Vol 85(10): 3435-3439 [1988]) and Sporn *et al.* (The Journal of Clinical Investigations, Vol 78: 329-332 [1986]). New claims 56-61 are rejected for the reasons set forth in the 35 U.S.C. 103(a) rejection in the Office Action of 4 April 2005, and for the reasons to be discussed in response to Applicant's arguments below.

Applicant argues that they have demonstrated a direct interaction between PDGFR and PI3-kinase that occurs in the kinase insert region of the PDGFR around Tyr751. Applicant argues that their in vitro system allows them to study the interaction between PDGFR (B form) and PI3-kinase, and to examine the requirement for phosphorylation of specific residues and conformational requirement for recognition. Applicant argues that the cited references fail to suggest the claimed methods. Applicant's arguments have been fully considered but have not been found to be persuasive.

Kazlauskas *et al.* teaches a basic methodology of immunoproecipitation, in vitro phoophosorylation to assess kinase activity, and gel electrophoresis to examine the association between activated PDGFR and the cellular proteins thought to be involved in transduction of growth signals. Kazlauskas *et al.* teach a method for detecting an association of PI3 kinase activity with PDGFRs. Figures 7 and 8 show the results of immunoprecipitation and PI3-kinase assays to determine the PDGF-dependent association of PDGFR with cellular polypeptides and PI3-kinase activity. Applicant's claim is drawn to a method of selecting a molecule that inhibits the binding of PI3-kinase to a PDGFR polypeptide. The methods described by Kazlauskas *et al.* can be easily employed as a method for screening compounds that inhibit the binding of two polypeptides, with one of the polypeptides being PDGFR. In addition, Kazlauskas *et al.* teach two tyrosine autophosphorylation sites (751 and 857) in the beta subunit of human PDGFR (Figures 1-3). They further perform receptor mutagenesis and expression experiments to study the functional significance of phosphorylation at these residues (Figures 5, 6), and PI3-kinase activity assays (Figures 7,8). Kazlauskas *et al.* conclude that PDGF-induced phosphorylation of Tyr0751 is critical for the association of an activated PI30kinase (p1128), clearly indicating a critical role for tyrosine phosphorylation in the kinase-PDGFR interaction. However, Kazlauskas *et al.* fail to explicitly teach application of their analysis to a screening method using receptor fragments, nor do they teach the specific PDGF receptor sequences in the claims disclosed in the present application.

In US Patent #6040149 (Filed 1/10/1997), Kolesnick *et al.* teach the methods of the present invention using fragments of growth factor receptors. Here, Kolesnick *et al.* define "polypeptide" as a single chain of amino acid residues, and give an example such as a Thr-Pro containing polypeptide that may be Thr-Pro or a larger polypeptide containing this amino acid sequence (claim 1). Kolesnick *et al.* further teach the polypeptide capable of being phosphorylated by the protein kinase as being Raf-1 or a portion thereof, or human EGF or a portion thereof (columns 13, 14; claims 2 and 3). Kolesnick *et al.* teach immunoprecipitation of Raf-1, or a portion thereof, followed by immune-complex kinase assay. Thus, Kolesnick *et al.* teach the use of fragments of the growth factor receptor in determining interaction of growth factor receptor with kinase protein.

As discussed in the Office Action of 4 April 2005, Gronwald *et al.* teach a PDGF receptor sequence that is 99.9% identical to SEQ ID NO: 4. Even though the sequence is not 100% identical to SEQ ID NO: 4, for the reasons stated in the previous Office Action, it is identical enough so as not to make the sequence or the method novel.

Finally, as previously discussed in the Office Action of 4 April 2005, Sporn *et al.* establish the involvement of PDGF in several types of cancers (p330). Further, Sporn *et al.* teach that growth factor antagonists present a viable approach in treatment of disease (p331).

Therefore, it would have been obvious to a person of ordinary skill in the art to combine the teachings of Kazlauskas *et al.*, Kolesnick *et al.* and Sporn *et al.* to screen for compounds that inhibit the binding between a PDGF receptor and PI3-kinase using

the PDGF receptor sequences taught by Gronwald *et al.* A person of ordinary skill in the art would have been motivated to combine the teachings because Kazlauskas *et al.* provide the methods for screening compounds and Sporn *et al.* teach that PDGFR signaling is involved in cancer, and thus antagonists might be a useful therapeutic intervention. The methods used by Kazlauskas *et al.* are standard and reproducible, and a high expectation of success would be reasonably assured. Kolesnick *et al.* provide the motivation to use various fragments of the PDGFR.

Applicant argues that the present invention is unique in that it teaches direct interaction between the PI3-kinase and PDGFR, and the specific residues involved. While applicant has interesting results or scientific merit, in light of the prior art presented above, Applicant's invention is obvious. The teachings of the prior art show that there is an interaction between PI3-kinase and PDGFR upon receptor activation (Kazlauskas *et al*, p1129). Applicant has shown that certain tyrosine residues appear integral to this interaction, but the interaction was already known at the time of invention. It would have been obvious to develop a method to screen for molecules that inhibit the binding between PDGFR and PI3-kinase to develop antagonists to inhibit the binding interaction. Applicant asserts that Kazlauskas *et al.* do not disclose the region of the receptor that participates in the binding interaction. Kazlauskas *et a*l. teach "autophosphorylation of the PDGFR in the kinase insert region regulates interaction with cell proteins (title)." In their experimentation, Kazlauskas *et al.* identify two tyrosine autophosphorylation sites in the beta subunit of PDGFR. They go on to describe receptor mutants with these sites, and perform experimentation with these mutants.

Thus, Kazlauskas *et al.* clearly provide guidance towards regions that would be obvious to use in a screening method. Further, although they did not determine the effects of phosphorylation at residue 740 on the binding interaction, Kazlauskas *et al.* present evidence that phosphorylation is required for PDGFR activity. In particular Kazlauskas *et al.* point out that PDGFR phosphorylation affects its association with other cell proteins. In particular, they point out that a kinase-inactive PDGFR does not have associated PI3-kinase activity, and that mutations of Tyr751 to Gly or Phe abolished interactions with the 120, 84 and 72 kDa associated proteins and PI3-kinase activity (1129, right column). Kazlauskas *et al* suggest a conformational change as being important in the interaction. Again, Applicant's finding are interesting research results, but do not add anything patentably non-obvious over the prior art.

Finally, Applicant still asserts that the secondary references do not add to the teachings of Kazlauskas *et al.* Sporn *et al.* present the motivation to develop the method, teaching that PDGFR signaling is involved in malignant transformation and may be a useful target for antagonists. Gronwald *et al.* teach SEQ ID NO: 4.

Conclusion

NO CLAIMS ARE ALLOWED.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Alexandra Zoltan-Jones, PhD whose telephone number

is (571) 272-3325. The examiner can normally be reached on Monday-Friday, 9am - 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa can be reached on (571) 272-0829. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

AZJ

LORRAINE SPECTOR
PRIMARY EXAMINER